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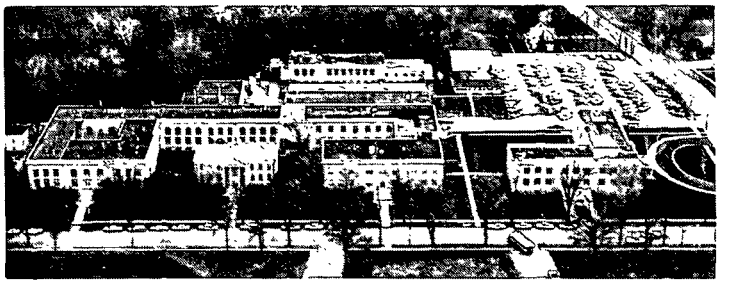

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THE PEROXYACETIC ACID OXIDATION OF A LIGNIN–RELATED β–ARYL ETHER

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INTRODUCTION

Oxidizing agents, such as hydrogen peroxide, chlorine, and potassium permanganate tend to be selective delignification agents. Among these, peroxyacetic acid is one of the most selective. Such selectivity makes it valuable for pulping and bleaching. Unfortunately, cost has prevented its commercial utilization.

This manuscript describes reactions of peroxyacetic acid with a compound which is a model for lignin. Reaction products are identified, and possible mechanistic pathways are proposed. In addition to providing insight into the way this reagent works, this research should be of value in comparing the mechanisms for various oxidative delignifying agents.

A more detailed account of this work is contained in the Ph.D. thesis by W. J. Lawrence.

This paper has been submitted for publication in Svensk Papperstidning.

THE PEROXYACETIC ACID OXIDATION OF A LIGNIN-RELATED β-ARYL ETHER

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ABSTRACT

The peroxyacetic acid oxidation of a β-aryl ether, 1-(3,4-dimethoxyphenyl)-2-(2-methoxy-4-methylphenoxy)propanol in acetic acid/water (19/1) at 25°C was investigated using a 5:1 molar ratio of peroxyacid to substrate. Following preliminary extractive and column chromatographic fractionation, pure samples of the oxidation products or their trimethylsilyl derivatives were isolated by preparative gas chromatography and identified by proton magnetic resonance and mass spectrometry. The oxidation products were quantitatively determined by gas chromatography of their trimethylsilyl derivatives.

The products indicated there were three major routes that resulted in direct cleavage of the interaryl linkage in this model compound. Two of these routes involved cleavage of the β-aryl ether bond, and the third was due to side-chain displacement. A fourth cleavage reaction involved initial oxidation of the benzylic hydroxyl to a carbonyl and subsequent Baeyer-Villiger oxidation to cleave the interaryl linkage. The isolation of a number of veratryl products from these reactions shows that demethoxylation is not necessary for the occurrence of these cleavage reactions.

Other major reactions of this system resulted in demethoxylation and/or ring hydroxylation and ring cleavage to muconic acids. The isolation of a methyl ester oxidation product suggests that ring cleavage can occur without complete demethoxylation.

INTRODUCTION

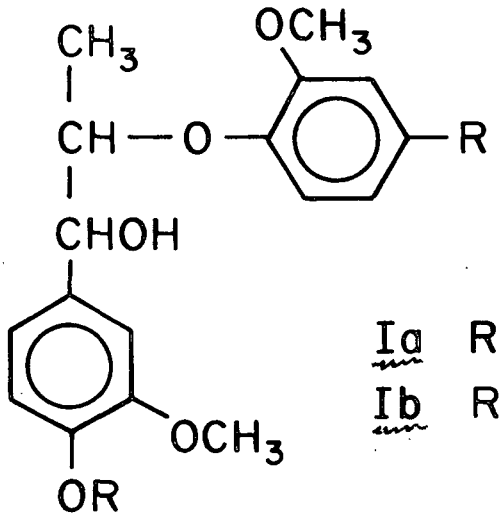
Following the early work of Poljak (1,2), peroxyacetic acid (PA) has been shown to be an effective delignification reagent by a number of workers (3-5). This effectiveness is due to the low reactivity with carbohydrates (6,7) and the high reactivity with the electron-rich sites such as olefinic, carbonyl and aromatic ring structures that are found in lignin. The reactions of peroxy acids with olefins (8) and carbonyl compounds (9) have been reviewed in the literature, and studies with aromatic compounds (10,11) indicate that their reactions involve a stepwise addition of OH^+ to the aromatic ring structure (12).

Farrand's study (10) of the PA oxidation of a number of substituted 4-methylphenols indicated that oxygen-containing substituents direct initial hydroxylation ortho and para to give o- and p-quinones. Whereas the p-quinones were relatively stable to excess PA, the o-quinones were readily oxidized to muconic acids. This study also showed that the rate of PA reaction was considerably increased by the introduction of a second oxygen-containing substituent in the aromatic ring and that free phenolic compounds reacted faster than their corresponding methyl ethers.

In a series of papers on the PA oxidation of β-aryl ether model compounds, Oki, et al. (13-15) proposed that the major reactions were demethoxylation and β-ether cleavage. Thus, veratrylglycerol-β-guaiacyl ether was demethoxylated to give guaiacylglycerol-β-guaiacyl ether and subsequent β-ether cleavage. Minor reactions involved loss of the hydroxymethyl group and oxidation of the benzylic hydroxyl to carbonyl followed by Baeyer-Villiger oxidation to 2-(2-methoxyphenoxy)acetic acid.

Sakai, et al. (16) have studied the PA oxidation of several β-aryl ether model compounds. In addition to demethoxylation and β-aryl ether cleavage to yield guaiacol, side-chain displacement to give α-guaiacoxy aldehydes was also a major reaction. They proposed 1-(4-hydroxy-3-methoxyphenyl)propan-1,2-diol as an oxidation product of 1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propanol (Ia) but were unable to confirm its presence.

All of these studies were characterized by low total yields of numerous identifiable products, thus attesting to the complexity of the reactions involved. With the acquisition of a mass spectrometer and a Fourier Transform nuclear magnetic resonance (NMR) spectrometer, the PA oxidation of a β-aryl ether model compound, representative of the most common inter-monomer in lignin (17), was further investigated. The model selected for this study, 1-(3,4-dimethoxyphenyl)-2-(2-methoxy-4-methylphenoxy)propanol (Ib) is shown below.



Ia R = H
Ib R = CH_3

The dimethyl ether was selected because the majority of similar aromatic groups in lignin are also etherified (17), although not in this manner. The methyl group para to the β-aryl ether bond was included to restrict reactions at this position (10,18) and also assure oxidation product differentiation between β-aryl ether cleavage and side-chain displacement, both of which could otherwise result in substituted p-quinone products. The γ-methyl group (rather than hydroxymethyl) in the side chain was chosen to reduce minor side reactions (14,15) and thus emphasize the reactions of interest.

RESULTS AND DISCUSSION

The synthetic route used to prepare Ib (see Experimental) led to a predominance of the erythro isomer in agreement with results reported in the literature (19). The mixture of isomers of Ib used in this study was 94% erythro as determined by proton NMR analysis of the acetates.

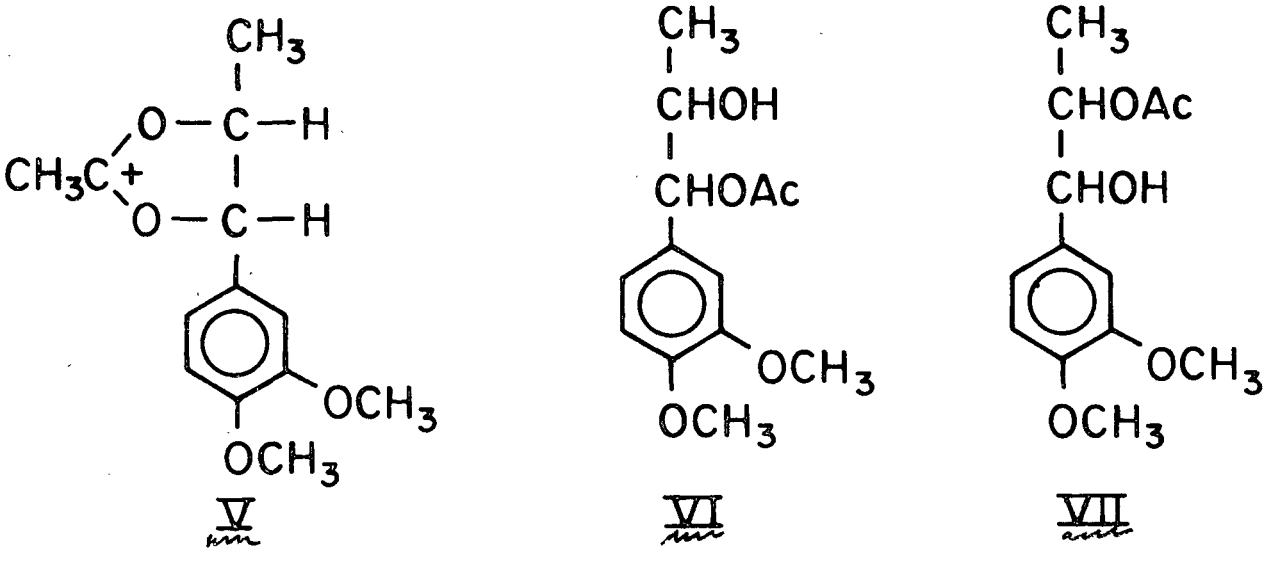
Model compound Ib was oxidized in 2.5% PA in acetic acid/water (19:1) using a 5:1 molar ratio of oxidant to substrate. After 24 hours, the excess PA was reduced with a minimum of sodium sulfite and the products extractively separated into neutral-phenolic and acidic fractions. Following fractionation by column chromatography, the product fractions were silylated and further separated into individual components by preparative gas chromatography. NMR and mass spectra were then obtained on the silylated derivatives. Product identification was made on the basis of these spectra and comparison to known spectra and GLC retention times where knowns were available.

Based on the reaction products identified, the PA oxidation of Ib can be divided into several types: β-ether cleavage, side-chain displacement, α-hydroxyl oxidation, and demethoxylation and/or ring hydroxylation, as shown in Fig. 1.

[Fig. 1 here]

Cleavage of the β-aryl ether bond could be attributed to two separate pathways. The first involves oxidative cleavage of Ib to yield 1-(3,4-dimethoxyphenyl)propan-1,2-diol (II) and 4-methyl-o-benzoquinone (III). Two possible mechanisms are shown in Fig. 2. Both mechanisms involve initial delivery of OH^+ to an oxygen-substituted position on the creosol ring and reaction with water. The quinone III, which is very reactive with PA (10), could not be isolated and was likely oxidized to 3-methylmuconic acid (IV), which was identified. Neighboring group participation (Path A) becomes even more favorable if acetylation of the benzylic hydroxyl of Ib occurs, as the positive charge can be delocalized more by participation of the acetoxy rather than hydroxy group, giving acetoxonium ion V. The isolation of small amounts of the monoacetate derivatives, VI and VII, could be due to hydrolysis of intermediate V.

[Fig. 2 here]



The mixture of erythro and threo isomers of II given in Table 1 show an erythro-to-threo ratio of 10:1, which is similar to the ratio in the starting material. Both mechanisms shown in Fig. 2 can account for the observed retention of configuration. Retention of configuration is contrary to that expected from carbonium ion formation in the side chain. Approach of water from the least hindered side would produce threo. This type of β-ether bond cleavage to give a side-chain diol has been proposed (16) but not demonstrated for the PA oxidation of β-aryl ether model compounds.

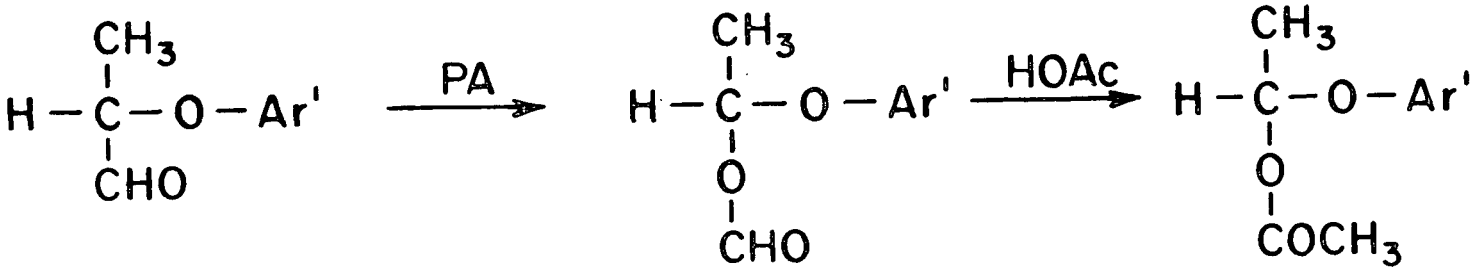
[Table 1 here]

The second type of β-aryl ether cleavage found in this study is analogous to that proposed by previous workers (13-16) and results in the formation of creosol (VIII) and 1-(3,4-dimethoxyphenyl)-1-hydroxypropan-2-one (IX). The mechanism proposed for this reaction is shown in Fig. 3. While others (13-16) have isolated the phenolic products due to this cleavage, the corresponding ketol product has not been previously reported. The isolation of ketol IX in this study further supports the mechanism shown in Fig. 3.

[Fig. 3 here]

The possibility of hydrolytic cleavage of Ib to give II and VIII was ruled out by treating Ib for 48 hours in the same reaction medium used in this study except containing no PA. The complete recovery of Ib under these conditions showed that Ib was not subject to any substantial amount of hydrolytic cleavage.

A third type of direct interaryl bond cleavage of Ib is due to side-chain displacement by PA to give 2-(2-methoxy-4-methylphenoxy)propionaldehyde (X) and 3,4-dimethoxyphenol (XI). These results are similar to those reported by Sakai, et al. (16), and the mechanism proposed for this reaction is shown in Fig. 4. In addition, two further reaction products of aldehyde X, 1-(2-methoxy-4-methylphenoxy)ethyl formate (XII) and 1-(2-methoxy-4-methylphenoxy)-ethyl acetate (XIII) were also isolated. These can be rationalized in terms of a Baeyer-Villiger oxidation and subsequent trans-esterification, respectively, as shown below.



X XII XIII

While Sakai, et al. (16) had identified structures analogous to X and XIII, the isolation of the phenol XI and the hemiacetal formate XII in this study provide additional evidence for this pathway.

[Fig. 4 here]

A fourth type of reaction of Ib was the oxidation of the benzylic hydroxyl to form ketone XIV. This type of reaction has been previously reported (13,20), and the mechanism for its formation is not known but may involve a free radical reaction (21,22).

The other major reaction of PA with Ib involved demethoxylation and/or ring hydroxylation. Several "monomeric and dimeric" products typical of this type of reaction were found in this study (23). While the spectral evidence indicated their presence, exact structures could not be proved in most cases, due to the possibility of positional isomers.

Oxidation of aromatic compounds by PA to muconic acids has been shown in many studies, and the isolation of IV in this study is not surprising. The isolation of 5-carboxymethyl-4-methyl-2(5H)furanone, XV, in this study suggests that ring opening to muconic acids may occur without complete demethoxylation to an o-quinone.

Quantitative results for the oxidation products are given in Table 1. The presence of a significant number and amount of products containing a veratryl aromatic ring shows that other types of PA reactions of Ib can occur without prior demethoxylation. The total yield of products is low, and this is likely due to the formation of low molecular weight fragments and quinone polymerization products.

The half-lives of Ib, II and IX under the oxidative conditions used in this study were 23.5, 60, and 1.25 hours, respectively. Comparison of the half-lives of Ib and II suggests that a substantial portion of the PA reactions of Ib are involved with oxidation of the creosol ring. The high reactivity of IX shows that the amount of IX formed in the PA oxidation of Ib was substantially greater than that indicated by the quantitative results given in Table I.

With the exception of III which was not isolated, the NMR and mass spectral data for the oxidation products and Ib are given in Tables II and III. While the mass spectrum of XIV does show a substantial number of fragment ions due to the trimethylsilyl (TMS) ether of Ib, the fragment ions at m/e 330, 194, 165, and 138 in addition to evidence provided by gas-liquid chromatography (GLC) retention times and thin-layer chromatography (TLC) R_f values and color reactions do support its presence as an oxidation product of Ib.

[Tables II and III here]

CONCLUSIONS

The results of this study show that there are at least five major types of primary oxidation reactions of β-aryl ether type compounds with peroxyacetic acid. Three of these reactions lead to direct cleavage of the interaryl linkage between the two aromatic nuclei.

Two of the cleavage reactions involve separate mechanisms and lead to different oxidation products as a result of cleavage of the β-aryl ether bond. The third cleavage reaction results in electrophilic displacement of the propyl side chain.

A fourth and indirect cleavage reaction of this type of compound involves oxidation of the benzylic hydroxyl to a carbonyl and subsequent Baeyer-Villiger

oxidation to an ester which can be cleaved hydrolytically. These cleavage reactions can occur without displacement of an ether group para to the propyl side chain.

Other significant reactions of this system are demethoxylation and/or ring hydroxylation and ring cleavage to muconic acids.

EXPERIMENTAL

General Methods

Melting points were determined on a Thomas-Hoover capillary apparatus. Measurement of pH was made with a Beckman Model 96 pH meter. Infrared spectra were taken on a Perkin-Elmer Model 700 recording spectrophotometer. TLC was performed on microscope slides coated with silica gel G (Brinkmann Inst.). Visualization was by (A) spraying with 20% (v/v) sulfuric acid in methanol followed by charring on a hot plate; (B) spraying with 2,4-dinitrophenylhydrazine agent (24). Column chromatography was performed with silica gel (60-200 mesh chromatographic grade, Sargent-Welch). Proton NMR spectra were taken with a Varian A-60A (60 MHz spectra) and a Jeol FX100 FT-NMR (100 MHz spectra) in $CDCl_3$ using tetramethylsilane and chloroform as internal standards. All oxidation products were 100 MHz spectra. Silylated products were in neat $CDCl_3$ using the $CHCl_3$ peak at 7.24 δ as reference.

Gas Chromatography

Preparative GLC was done on a Varian Aerograph 200 equipped with a thermal conductivity detector using 5 ft and 10 ft x 0.25 inch stainless steel columns packed with 5% OV-17 on 80/90 mesh Anakrom ABS. Product samples were collected in 4 mm o.d. glass U-tubes, stored in a desiccator over P_2O_5 and transferred with appropriate deuterated solvent just prior to NMR analysis.

Qualitative and quantitative GLC were done on a Varian Aerograph 1200 instrument equipped with a hydrogen flame-ionization detector. Columns were packed in 0.125 inch stainless steel tubing arranged for on-column injection. The following conditions were employed: (A) 5% SE-30 on 60-80 mesh AW/DMCS Chromosorb W (4 ft); nitrogen, 30 mL min^{-1}; column, 230°; injector, 270°; detector, 270°C; (B) 10% SE-30 on 90/100 mesh Anakrom SD (10 ft); nitrogen, 30 mL min^{-1}; column, 130° for 6 min, then programmed 2° min^{-1} to 170°; injector, 220°; detector, 250°C; (C) 5% OV-17 on 80/90 mesh Anakrom ABS (5 ft); nitrogen, 20 mL min^{-1}; column, 100° for 6 min, then programmed 2° min^{-1} to 230°; injector, 270°; detector, 300°C.

Gas Chromatography-Mass Spectrometry

Mass spectra were determined with a Du Pont Instruments 21-491 spectrometer interfaced with a Varian Aerograph 1400 gas chromatograph. Columns used were 5 ft and 15 ft x 0.125 inch stainless steel tubing arranged for on-column injection, packed with 3% OV-17 on 80/100 mesh Supelcoport. Helium (UHP Helium, minimum purity 99.999%, Matheson Gas) was used as the carrier gas and perfluorokerosene (PCR, Inc.) used for mass reference. The filament was in GC mode, resulting in current of 50 μamps and 75 volts when scanning and 20 volts when not scanning.

Chemicals

Guaiacol, creosol (VIII), benzyl bromide, propionyl chloride, acetovanillone, ethyl 2-bromopropionate, veratraldehyde, adipic acid (XVI), 1-(3,4-dimethoxyphenyl)propan-2-one, 3',4'-dihydroxypropiophenone (XVII), Tri-Sil concentrate, N,O-bis-trimethylsilyltrifluoroacetamide (BSTFA) and silylation grade N,N-dimethylformamide were available from commercial sources. cis,trans-3-Methylmuconic acid (IV) was available from a previous study (10).

The following compounds were prepared as previously described in the literature: methoxyhydroquinone (XVIII), (25); 3,4-dimethoxyphenol (XI), (26); 1-(3,4-dimethoxyphenyl)-1-hydroxypropan-2-one (IX), (27); 2-bromopropioveratrone (28); propiovanillone (XIX), (29) and 1-(3,4-dimethoxyphenyl)ethanol (XX), (30), and their physical constants were in good accord with literature values. 1-(3,4-Dimethoxyphenyl)propan-1,2-diol was prepared according to Hibbert (28), and its melting point, 122-123°C, identified the product as the erythro isomer (31).

Acetylated derivatives of Ib, VIII, XI, and XVIII were prepared by reaction of the substrate (10-30 mg) with acetic anhydride (1.5 mL) in pyridine (6 mL) overnight. The solution was diluted with chloroform (30 mL) and extracted with 1N hydrochloric acid (3 x 50 mL) and distilled water (3 x 50 mL), dried and evaporated *in vacuo*.

3',4'-Dimethoxypropiophenone (XXI). This compound was prepared in 85% yield from XVII or XIX by the alkylation method of Buck (32). Crystallization from ether-petroleum ether gave a white crystalline product of m.p. 59-60°C. (Literature: m.p. 59-60°C (28)).

4'-Benzyloxy-3'-methoxypropiophenone (XXII). Equimolar amounts of the sodium salt of propiovanillone and benzyl bromide were allowed to react for 2 hours in N,N-dimethylformamide and were worked up according to the procedure of Miksche, *et al.* (33). Crystallization from isopropanol gave 16.9 g (94.5% yield) of white crystalline material, m.p. 94.5-96°C. (Literature: m.p. 92-94°C (34)).

2-(2-Methoxy-4-methxylphenoxy)propanoic Acid (XXIII). This compound was prepared from ethyl 2-bromoproionate and creosol (VIII) by the general procedure

of Fredga (35). Crystallization from methanol gave a 69.4% yield of white crystalline material, m.p. 111.5-112°C. (Found: C, 62.85; H, 6.66. $C_{11}H_{14}O_4$ requires C, 62.84; H, 6.71%). ^{1}H NMR (60 Mhz, $CDCl_3$): δ 1.63 (d, CH_3, 3H, J=7 hz), 2.30 (s, ϕ-CH_3, 3H), 3.85 (s, OCH_3, 3H), 4.63 (q, CH, 1H, J=7 hz), 6.6-7.0 (m, arom, 3H), 10.23 (s, CO_2H, 1H).

2-(2-Methoxy-4-methylphenoxy)propanol (XXIV). A solution of 5.0 g of XXIII in 100 mL of anhydrous ether was added dropwise to a stirred suspension of 2.0 g of lithium aluminum hydride in 200 mL of anhydrous ether. After addition was complete, the solution was stirred for an additional 4 hours; then ethyl acetate (50 mL) was added dropwise. After addition of distilled water (200 mL), the layers were separated, the aqueous layer was further extracted with ether (3 x 40 mL), and the combined ether fractions were dried, concentrated and distilled (85-86°C, 0.025 mm) to give 85.7% yield of a colorless liquid. ^{1}H NMR (60 Mhz, $CDCl_3$): δ 1.30 (d, CH_3, 3H, J=6 hz), 2.28 (s, Ar-CH_3, 3H), 3.17 (s, OH, 1H), 3.62 (t, CH_2, 2H, J=5 hz), 3.80 (s, OCH_3, 3H), 4.20 (m, CH, 1H), 6.5-7.0 (m, arom, 3H).

2-(2-Methoxy-4-methylphenoxy)propionaldehyde (X). To a stirred solution of 35 g of dipyridine chromium trioxide (36) in 700 mL of anhydrous dichloromethane (37) at 10°C was added 4 g of XXIV in 50 mL of anhydrous dichloromethane. The temperature was allowed to rise to 25°C. It was stirred for an additional 1/2 hour, and then the solution was decanted off. The residual black tar was extracted with dichloromethane (4 x 50 mL), and the combined organic fractions were washed with 5% sodium hydroxide (3 x 100 mL), 5% hydrochloric acid (3 x 100 mL), and saturated sodium bicarbonate (3 x 100 mL), dried, and evaporated *in vacuo* to an orange oil. Distillation (60-62°C, 0.025 mm) gave 1.8 g (45% yield) of a colorless liquid. (Found: C, 68.03; H, 7.49.

$C_{11}H_{14}O_3$ requires C, 68.02; H, 7.26%). ^{1}H NMR (60 Mhz, $CDCl_3$): δ 1.45 (d, CH_3, 3H, J=7 hz), 2.30 (s, φ-CH_3, 3H), 3.83 (s, OCH_3, 3H), 4.48 (q of d, CH, 1H, J= 1.5, 7 hz), 6.6-7.0 (m, arom, 3H), 9.83 (d, CHO, 1H, J=1.5 hz).

3',4'-Dimethoxy-2-(2-methoxy-4-methylphenoxy)propiophenone (XIV). Equimolar amounts of the sodium salt of creosol and 2-bromopropioveratrone were allowed to react for 2 hours on a steam bath in N,N-dimethylformamide and worked up according to the procedure of Miksche, et al. (33). Crystallization from ether-petroleum ether gave 85% yield of white crystalline material, m.p. 92-93°C. (Found: C, 69.34; H, 6.83. $C_{19}H_{22}O_5$ requires C, 69.07; H, 6.71%). ^{1}H NMR (60 Mhz, $CDCl_3$): δ 1.68 (d, γ-CH_3, 3H, J=7 Hz), 2.26 (s, φ-CH_3, 3H), 3.83, 3.95 (s, OCH_3, 9H), 5.40 (q, β-CH, 1H, J=7 hz), 6.6-7.0 (m, arom, 4H), 7.7-8.0 (m, arom, 2H).

1-(3,3-Dimethoxyphenyl)2-(2-methoxy-4-methylphenoxy)propanol (Ib). To a stirred solution of 2.0 g of XIV in 150 mL of anhydrous ethanol was added 4.0 g of sodium borohydride. The solution was stirred for 2 hours, distilled water (200 mL) was added, and the product was extracted with chloroform (3 x 100 mL). The chloroform solution was washed with distilled water (3 x 100 mL), dried and evaporated in vacuo. Crystallization from ether-petroleum ether gave a crystalline hydrate, m.p. 67-71°C. Subsequently a nonhydrated crystalline form was obtained of m.p. 85-86°C. (Found: C, 68.46; H, 7.29. $C_{19}H_{24}O_5$ requires C, 68.65; H, 7.23%). ^{1}H NMR (60 Mhz, $CDCl_3$): δ 1.17 (d, γ-CH_3, 3H, J=6.5 hz), 2.33 (s, φ-CH_3, 3H), 3.50 (s, OH, 1H), 3.83 (s, OCH_3, 9H), 4.33 (m, β-CH, 1H), 4.85 (d, α-CH, 1H, J=4 hz), 6.7-7.1 (m, arom, 6H). A single large batch of Ib (9.4 g) was prepared, and portions of this material were used in the PA oxidations reported in this paper. A portion of this material was acetylated as described previously, and NMR analysis (100 Mhz) indicated it to be 94% erythro and 6% threo by the ratio of the integral values of the acetyl signals at 2.10 and 2.00 δ, respectively (38).

Peroxyacetic acid was freshly prepared before each oxidation by the hydrogen peroxide oxidation of acetic acid with sulfuric acid catalyst (39). The distilled PA (approximately 35% PA, 0.1% hydrogen peroxide, 5% acetic acid, and 60% water) was diluted to 20% with glacial acetic acid and stored at 5°C. All glassware contacting PA solutions was passivated to prevent excess decomposition (39).

Oxidation Conditions

The PA oxidations were run in glass-stoppered flasks in a constant temperature bath at 25°C. The substrate and an appropriate amount of glacial acetic acid were added, and the solutions were equilibrated for 1/2 hour during which time the substrate was completely dissolved. At this time an appropriate amount of the freshly prepared PA solution was added to give a 5:1 molar ratio of oxidant to substrate, a final PA concentration of 2.5% by weight, and an acetic acid/water ratio of 19/1 by weight. The solutions were swirled and aliquots for zero-time samples were taken for PA and substrate analyses. Subsequently, aliquots for PA, substrate, and product analyses were taken at appropriate times and analyzed as follows.

Workup Procedures

Duplicate 1-mL aliquots for PA and hydrogen peroxide analyses were placed in tared 1-mL vials, reweighed, and analyzed by an iodimetric procedure (40). Typical values for initial hydrogen peroxide concentration were 0.010-0.015% by wieght. Control reactions were run without substrate to allow for estimation of the rate of decomposition of PA which was typically 1.9×10^{-3} wt.% hr^{-1}.

Duplicate 1-mL aliquots for analysis of residual Ib were placed in tared vials and reweighed; residual PA was reduced with a minimum of sodium sulfite as indicated by starch-KI test paper (Fisher Scientific). An appropriate

amount of internal standard solution (XXII in ethanol) was added, and the contents of the vial were transferred to a separatory funnel. Chloroform (20 mL) was added, and the solutions were washed with 5% sodium carbonate (3 x 20 mL) and distilled water (3 x 20 mL). The chloroform was dried, evaporated in vacuo, and the oil taken up in a minimal amount of chloroform and analyzed by GLC conditions A.

Duplicate aliquots for product analyses of Ib (5 mL) and substrate analyses of II and IX (1 mL) were placed in tared vials, reweighed, and residual PA was reduced as described above. Appropriate amounts of internal standard (XVI and XX for product analyses of Ib; XX for substrate analyses of II and IX) were added, and the solution was neutralized under a stream of nitrogen to pH 7.2-7.5 with sodium carbonate. The neutral-phenolic compounds were extracted with chloroform (10 x 25 mL), dried, and evaporated in vacuo. For acidic product analyses of Ib, the aqueous layer was acidified (pH 2, HCl) and evaporated in vacuo at 30°C to dryness. The acidic products were dissolved in distilled water (200 mL) and evaporated to dryness two times to remove excess acetic acid. The resulting product mixture was dissolved in distilled water (200 mL) and continuously extracted with ether for 24-36 hours.

The neutral-phenolic samples were dissolved in 0.2-0.4 mL of anhydrous chloroform (37); Tri-Sil concentrate, 0.5-0.7 mL, was added, and the mixture was allowed to react for 1 hour at 25°C. Products of Ib were analyzed by GLC conditions C and II and IX were analyzed by GLC conditions B. The acidic ether extracts were evaporated to dryness, dissolved in silylation grade N,N-dimethylformamide, 0.2-0.4 mL, and 75-150 μL of BSTFA was added. After reacting at 25°C for 1 hour, the samples were analyzed by GLC conditions C.

Qualitative Analysis

For qualitative analysis of the products of Ib, a sample was oxidized for 24 hours, and the entire sample was worked up into neutral-phenolic and acidic product fractions as described above. Subsequently, the neutral-phenolic and acidic fractions were chromatographed on a silica gel column. Eluents used: neutral-phenolic; benzene, isopropyl ether, ethyl ether, chloroform, ethyl acetate and acetone; acidic; ethyl ether:chloroform (1:1, v/v), chloroform, ethyl acetate, acetone, ethanol, distilled water:acetic acid (1:1, v/v). The first two neutral-phenolic fractions were analyzed directly, and all other fractions were derivatized as previously described. The various fractions were further fractionated into pure components by preparative GLC, and the components were analyzed by NMR and mass spectrometry. The retention times of the oxidation products were measured using GLC conditions C.

The column fraction containing XIV was also analyzed by TLC using isopropyl ether:ethyl ether (1:1, v/v). Oxidation product XIV gave the same R_f value (0.67) and color reactions with spray reagents A and B as an authentic sample of XIV. This additional proof of structure is given since the mass spectrum of product XIV showed fragment ions from the TMS ether of Ib due to its large tailing peak.

The column fraction containing IIa was evaporated to dryness. A portion was used for preparative GLC and subsequent NMR and mass spectral analyses. The remainder was crystallized from ethyl acetate and gave a crystalline product of m.p. 122-123°C whose infrared spectrum (KBr pellet) was identical to an authentic sample of IIb.

Stability of Ib in Reaction Medium

Samples of Ib were dissolved in 95% aqueous and glacial acetic acid at 25°C for 48 hours. Appropriate workup as described previously and analysis by GLC conditions A showed complete recovery of Ib.

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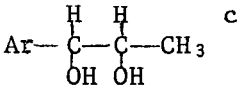
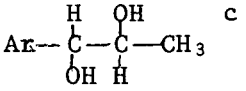
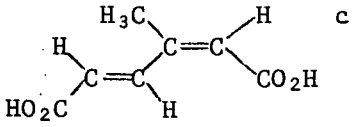
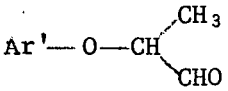
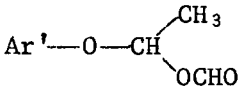
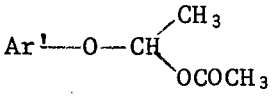
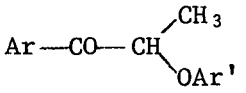
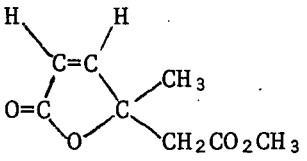
Table I. PA oxidation products[a] of Ib

Product	Structure	GLC ret. time (min)	Means of identification	Yield[b] (%)
IIa	 [c]	37.0	MS,NMR,IR,m.p., GLC ret. time	19.2
IIb	 [c]	38.5	MS,GLC ret. time	1.9
IV	 [c]	31.8	MS,GLC ret. time	2.3
VI	Ar—CHOAc—CHOH—CH_3 [c]	45.5,47.5	MS,NMR	VI + VII = 0.8
VII	Ar—CHOH—CHOAc—CH_3 [c]	44.5	MS,NMR	
VIII	Ar'-OH [c]	12.9	MS,NMR,GLC ret. time	8.5
IX	Ar—CHOH—CO—CH_3 [c]	40.0	MS,NMR,GLC ret. time	1.8
X		24.5	MS,NMR,GLC ret. time	X + XIII = 4.3
XI	Ar—OH [c]	21.5	MS,NMR,GLC ret. time	3.5
XII		21.5	MS,NMR	Trace
XIII		25.5	MS,NMR	X + XIII = 4.3
XIV		88.0	MS,GLC ret. time,TLC	Trace
XV		N.D.[d]	MS,NMR	Trace

[a] Ar = 3,4-dimethoxyphenyl; Ar' = 2-methoxy-4-methylphenyl.

[b] After 4 hours reaction time, based on consumed starting material, Ib.

[c] Identified as TMS derivative.

[d] N.D. = not determined.

Table II. ^{1}H NMR data of the PA oxidation products of Ib

Products	Chemical shifts (δ in ppm)					
	Aromatic H	Methoxyl H	H_α	H_β	H_γ	Others
IIa	6.87(m)(3H)	3.89(s)(6H)	4.31(d)(1H)	3.85(m)(1H)	1.21(d)(3H)	α-OTMS 0.05(s)(9H) β-OTMS -0.10(s)(9H)
VI	6.80(m)(3H)	3.88(s)(3H) 3.94(s)(3H)	5.40(d)(1H)	4.00(m)(1H)	1.12(d)(3H)	α-OAc 2.08(s)(3H) β-OTMS 0.01(s)(9H)
VII	6.80(m)(3H)	3.87(s)(6H)	4.51(d)(1H)	5.02(m)(1H)	1.01(d)(3H)	β-OAc 2.03(s)(3H) α-OTMS 0.03(s)(9H)
VIII	6.75(m)(3H)	3.86(s)(3H)	-	-	-	ϕ-CH_3 2.29(s)(3H) ϕ-OTMS 0.28(s)(9H)
IX	6.80(m)(3H)	3.87(s)(6H)	4.99(s)(1H)	-	2.08(s)(3H)	α-OTMS 0.12(s)(9H)
X	6.80(m)(3H)	3.84(s)(3H)	-	4.47(o)(1H)	1.46(d)(3H)	ϕ-CH_3 2.31(s)(3H) CHO 9.80(d)(1H)
XI	6.50(m)(3H)	3.82(s)(3H) 3.84(s)(3H)	-	-	-	ϕ-OTMS 0.25(s)(9H)
XII	6.85(m)(3H)	3.84(s)(3H)	-	6.50(q)(1H)	1.66(d)(3H)	ϕ-CH_3 2.31(s)(3H) O-CHO 8.00(s)(1H)
XIII	6.75(m)(3H)	3.83(s)(3H)	-	6.39(q)(1H)	1.62(d)(3H)	ϕ-CH_3 2.29(s)(3H) O-$COCH_3$ 2.01(s)(3H)
XV	2-H 6.05(d)(1H) 3-H 7.68(d)(1H) 4-CH_3 1.57(s)(3H) 5-H 2.64,2.95(AB doub.)(2H) CO_2CH_3 3.70(s)(3H)					

Table III. Mass spectrometrical data of Ib and its PA oxidation products

Compound	Derivative	Mass spectrometrical data
Ib	TMS ether	404 (2), 317 (5), 267 (3), 239 (100), 210 (16), 207 (40), 195 (7), 180 (8), 178 (7), 165 (9), 151 (6), 138 (4), 123 (7), 107 (9), 105 (8), 91 (16), 79 (9), 77 (13), 75 (18), 73 (96)
IIa	bis-TMS ether	356 (1), 341 (1), 267 (1), 239 (100), 193 (17), 165 (6), 147 (52), 117 (15), 105 (6), 73 (11)
IIb	bis-TMS ether	356 (0.5), 341 (2), 251 (3), 239 (100), 165 (8), 147 (46), 117 (9), 73 (49)
IV	bis-TMS ester	300 (3), 285 (16), 210 (7), 183 (100), 167 (8), 147 (46), 93 (8), 75 (22), 73 (55)
VI	TMS ether	326 (40), 282 (48), 267 (8), 266 (17), 194 (12), 167 (99), 166 (23), 165 (32), 151 (69), 117 (100), 75 (41), 73 (88), 45 (16), 43 (30)
VII	TMS ether	326 (12), 265 (2), 239 (100), 194 (7), 165 (10), 151 (13), 73 (11), 43 (8)
VIII	TMS ether	210 (16), 195 (10), 180 (100), 150 (7), 112 (8), 89 (10), 75 (7), 73 (27), 59 (9), 45 (22), 43 (8)
IX	TMS ether	282 (1), 267 (12), 239 (100), 165 (9), 73 (27), 43 (10)
X	-	194 (100), 165 (100), 150 (67), 138 (33), 137 (78), 123 (22), 109 (43), 107 (32), 91 (51), 77 (26)
XI	TMS ether	226 (100), 211 (55), 183 (9), 167 (6), 95 (13), 75 (27), 73 (76)
XII	-	180 (15), 138 (100), 123 (35), 95 (8), 87 (9), 85 (35), 83 (57), 77 (5), 49 (12), 48 (15), 47 (25), 43 (16) Molecular ion at m/e 210 was absent.
XIII	-	224 (1), 181 (20), 180 (16), 166 (28), 165 (19), 138 (100), 123 (36), 107 (7), 95 (8), 91 (9), 77 (8), 66 (8), 43 (37)
XV	-	170 (12), 155 (2), 139 (4), 123 (16), 113 (20), 111 (11), 97 (100), 65 (5), 59 (13), 55 (10), 54 (11), 43 (5)
XIV	-	330 (53), 194 (24), 178 (20), 165 (67), 151 (16), 150 (23), 138 (42), 123 (7), 91 (10), 77 (7) Peaks at m/e 404,267,239 and 73 due to Ib TMS ether impurity have been deleted.

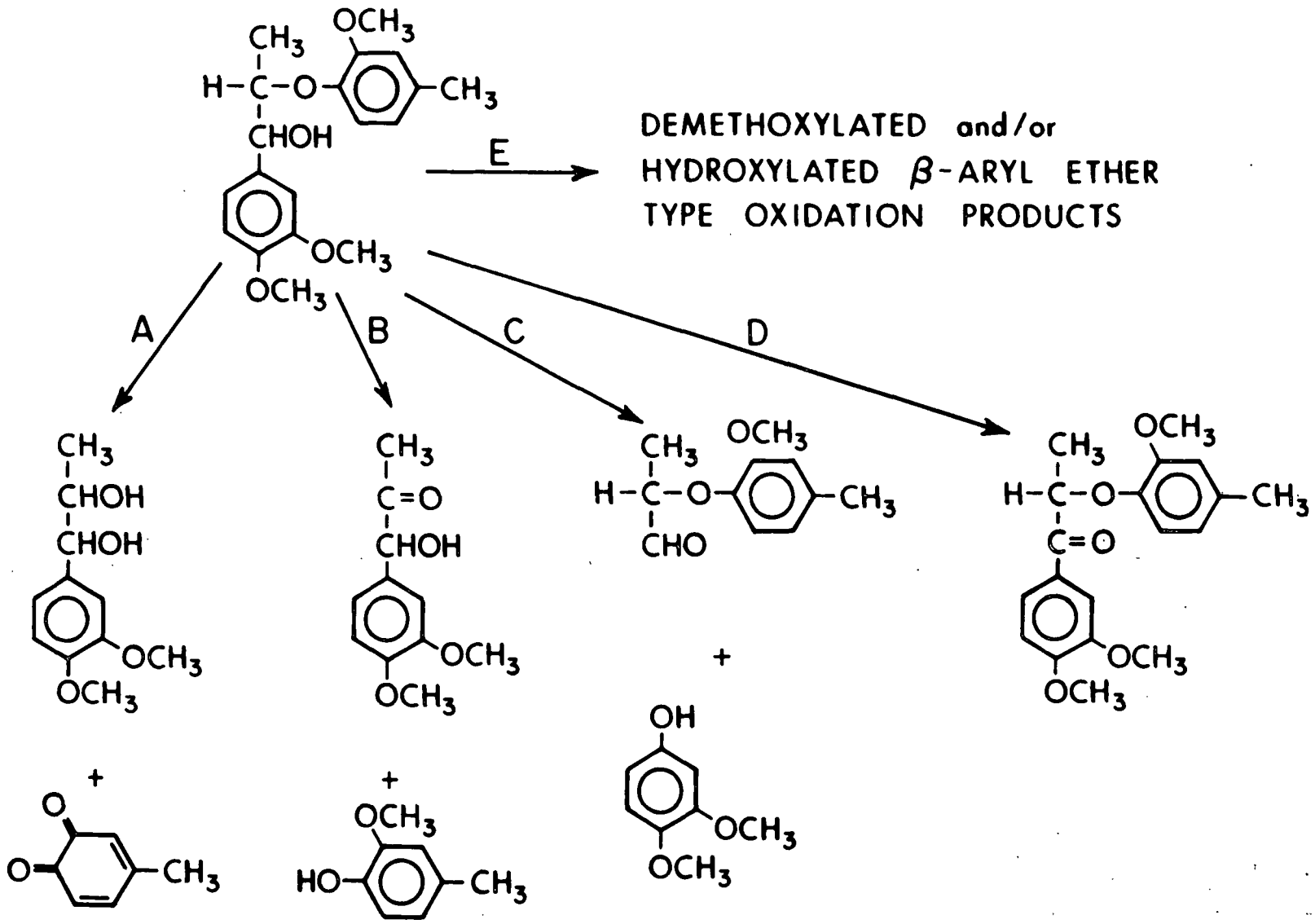


Figure 1. Major degradative pathways in PA oxidation of Ib.

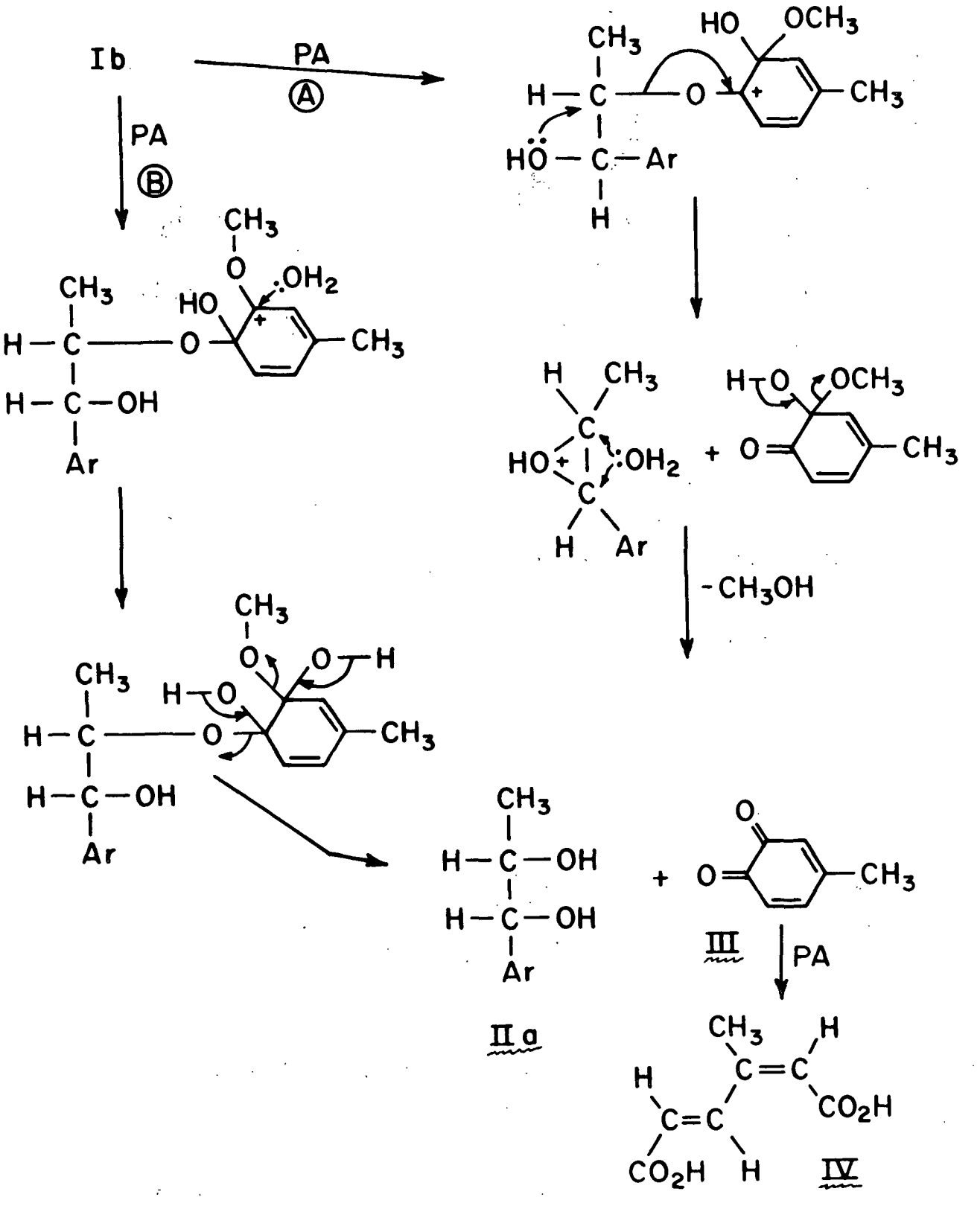


Figure 2. Possible mechanism for formation of diol II in PA oxidation of Ib.

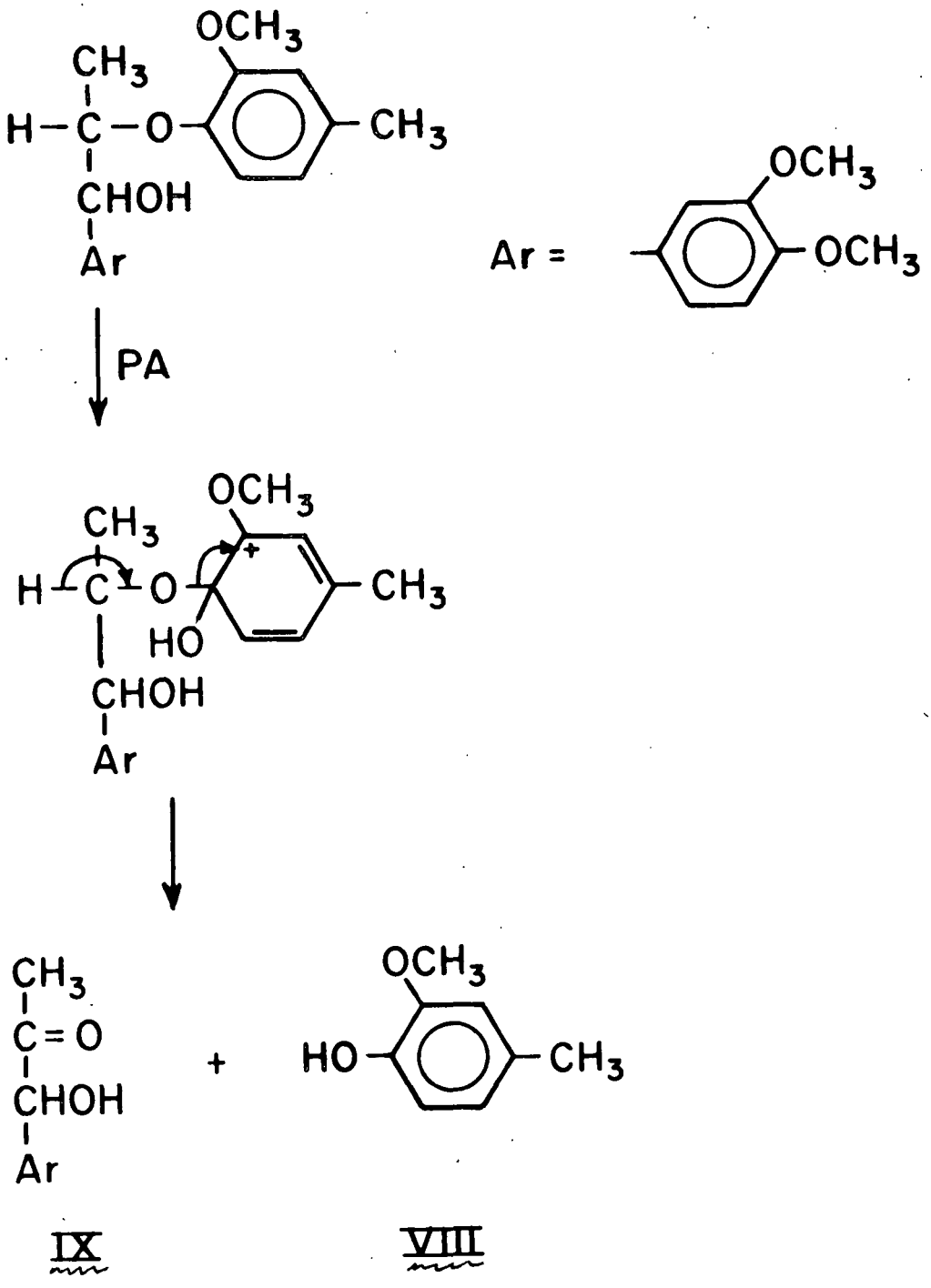


Figure 3. Possible mechanism for formation of ketol IX and creosol VIII in PA oxidation of Ib.

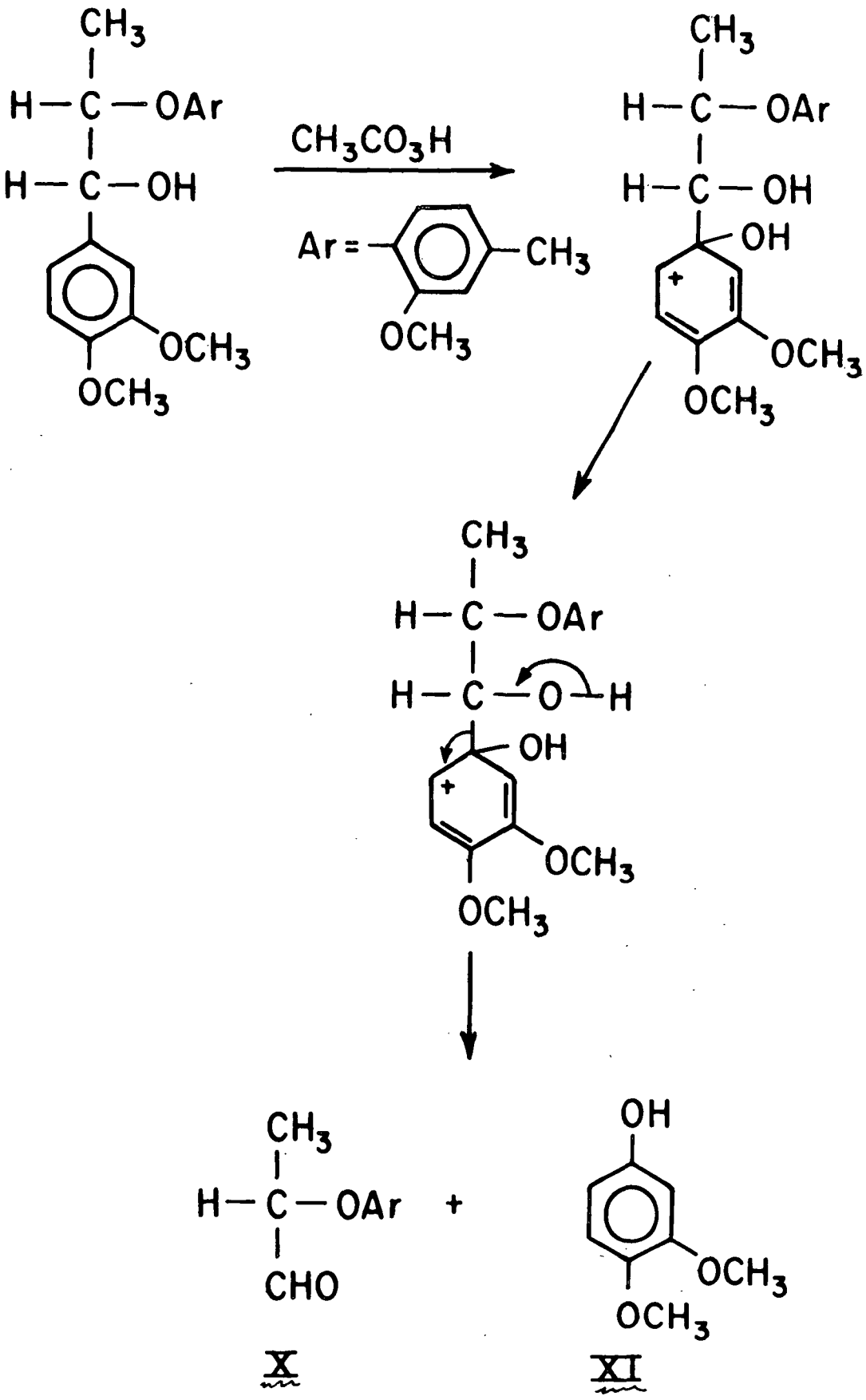


Figure 4. Possible mechanism for formation of aldehyde X and phenol XI in PA oxidation of Ib.